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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/581,402	06/12/2000	TETSUNORI FUJISAWA	2000_0562A	7196

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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1637	10

DATE MAILED: 05/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/581,402	Applicant(s) Fujisawa et al
	Examiner Jeffrey Fredman	Art Unit 1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *April 8, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *2-14* is/are pending in the application.

4a) Of the above, claim(s) *8-11 and 14* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2-7, 12, and 13* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 2-7, 12 and 13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

Here, the new limitation of "provided that a combination where R7 is methyl, R8 is methyl and R9 is methyl is excluded" in claims 2 appears to represent new matter. A careful review by the examiner of the specification failed to identify any support for this new negative limitation. No basis for the limitation was idenfied by the applicant in the response. As noted by MPEP 2173.05(I),

> " Any negative limitation or exclusionary proviso must have basis in the original disclosure. See Ex parte Grasselli , 231 USPQ 393 (Bd. App. 1983) aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure

should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement."

Since no basis has been found to support the new claim limitation in the specification, the claims are rejected as incorporating new matter.

3. Claims 2-7, 12 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds shown in Tables 1-3, does not reasonably provide enablement for the entire genus of structures which are potential matrix metalloproteinase inhibitors encompassed by the claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The nature of the invention is chemical, in an area where single structural substitutions may alter the function of the compound in unpredictable ways. The claimed invention is drawn broadly to any compound which falls within the genus disclosed by claim 1. While the specification provides substantial guidance on methods of making the chemical compounds and some guidance on the use of the working examples, a particular 40 or so compounds disclosed in tables 1-3 on pages 148-152 of the specification, the specification gives no guidance on the use of any compound outside of this set of compounds with regard to their function or efficacy. As noted, there are about 40 working examples. The prior art recognizes the extreme unpredictability in this area. In fact, Dickens et al (WO 94/02447), synthesizing extremely similiar compounds states regarding his compounds that "It has been found that such compounds have in

general the sought after but unpredictable combination of desirable formulation characteristics, including water-solubility, as well as desirable activity profiles as inhibitors of MMP's (page 4)". Dickens further notes that "Unfortunately, however, the physicochemical and/or pharmacokinetic properties of the specific compounds disclosed in those publications have generally been disappointing (page 2 last sentence to page 3)". Thus, Dickens notes that 12 different patents and published patent applications synthesized particular compounds, not simply a disclosure as here of broad generic structures, and these particular compounds were unpredictable in function and unable to achieve the sought after purpose of treatment. Further evidence of the unpredictability is provided by Brenner (WO 97/05865) who notes that it is desirable to identify inhibitors, but (prior to his work) "none of the inhibitors so far identified has proven an effective therapeutic for the treatment of collagen related diseases or even an inhibitor to C-proteinase activity (page 5, lines 2-4)". Crimmin et al (U.S. Patent 5,652,262) is currently cumulative over the Dickens prior art, but Crimmin teaches similar compounds and the unpredictability of such compounds (see column 2, lines 40-44). As shown by the art, this area is highly unpredictable and alteration of the compounds results in altered activities and altered formulation profiles which have entirely unpredictable results. It would require a very large amount of experimentation, amounting to the synthesis of a large number of representative compounds, followed by testing the compounds for activity in order to determine whether particular subelements of the genus claim are useful in metalloproteinase inhibitor assays. This amount of experimentation is not only inventive, but is sufficient to provide the material for multiple Ph.D theses and would be very expensive and time

consuming. Therefore, given the unpredictability of the art, the teachings in the art that this area is highly unpredictable, the broad claims, the large amount of experimentation necessary and the minimal guidance presented of essential elements which are required for function as opposed to 40 working examples and the relatively high level of skill in the art, it is concluded that, on balancing these factors, undue experimentation would be required to use the invention as claimed.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 2-7, 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Fujisawa et al (JP 8-53403)

Fujisawa teaches a compound with the structure of claim 2 as shown in columns 1-12.

This compound of Fujisawa, for example compound I in columns 1 and 2, teaches a situation which anticipates claim 2 where

Claim 2 structure	Fujisawa Reference Structure
R1 - hydrogen	R1 - Hydrogen (see columns 1-12)
R2 - hydrogen	R2 - Hydrogen (see columns 1-12)
R3 - C1-4 alkyl	R3 - Shows a C1 alkyl (see structure 1)
R4 - C3-9 alkyl	Has C4 alkyl at this position (see structure 1)
N-R5-R6	R5 can be amino methyl group (see columns 1-12)
R7-9 - Hydrogen or methyl	CH2R4 has two hydrogens and methyl

Fujisawa teaches that the compounds are matrix metalloproteinase inhibitors (abstract) and teaches pharmaceutically and veterinarily acceptable excipients and cariers (columns 1-12).

Allowable Subject Matter

6. The elected species, Compound 65, is novel and unobvious over the cited prior art, because none of the art teaches or suggests it's particular structure.

Response to Arguments

7. Applicant's arguments filed April 8, 2002, have been fully considered but they are not persuasive.

Applicant argues first that the claims are enabled. Applicant argues that complex experimentation does not render the claims non-enabled. Here, it is not just the complexity of the experimentation and the large quantity of experimentation which drives the conclusion of undue experimentation. The extremely high level of unpredictability, supported by references in the matrix metalloproteinase inhibitor art, is what leads to the conclusion of undue experimentation.

Applicant then relies upon In re Angstadt to argue that every species need not be covered. While this is correct insofar as it goes, it is noted that in Angstadt, no evidence other than the large number of species was provided to challenge enablement. In the current situation, several references in the exact same art demonstrate the unpredictability and large quantity of experimentation necessary to identify metalloproteinase inhibitors which would function. In a

later case, In re Vaeck, 947 F.2d 488, 496 (CAFC 1991), the Court stated "However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. Where, as here, a claimed genus represents a diverse and relatively poorly understood group of microorganisms, the required level of disclosure will be greater than, for example, the disclosure of an invention involving a "predictable" factor such as a mechanical or electrical element." Here, the genus represents a relatively poorly understood set of chemical entities which are intended to function to inhibit matrix metalloproteinases. Lastly, as noted in the rejection, the prior art of Dickens expressly refers to the current compounds as being unpredictable in activity.

With regard to the prior art rejections, the amendment has overcome the rejection applying Dickens, but a new rejection applying Fujisawa was necessitated.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman, Ph.D. whose telephone number is (703) 308-6568.

The examiner is normally in the office between the hours of 6:30 a.m. and 4:00 p.m., and telephone calls either in the early morning or the afternoon are most likely to find the examiner in the office.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Jeffrey Fredman
Primary Patent Examiner
Art Unit 1637

May 24, 2002